IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 7736
RASHTCHIAN *et al.*	Art Unit: 1634
Appl. No. 09/741,664	Examiner: Arthur, L.
Filed: December 21, 2000	Atty. Docket: 0942.3910003/BJD/AGU
For: **Stable Compositions for Nucleic Acid Amplification and Sequencing**	

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Amendment And Reply Under 37 C.F.R. § 1.111

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Office Action dated March 22, 2002 (Paper No. 6), Applicants submit the following Amendment and Remarks. This Amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.121 and MPEP § 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and

any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification:

Please substitute the first full paragraph on page 1 (at lines 7-10), with the following paragraph:

A1

This application is a continuation of U.S. Application No. 09/049,021, filed March 27, 1998 (now abandoned), which is a continuation-in-part of U.S. Application No. 08/801,720, filed February 14, 1997 (now abandoned), which is a continuation-in-part of U.S. Application No. 08/689,815, filed August 14, 1996 (now abandoned), the contents of which are fully incorporated herein by reference.

Please substitute the first full paragraph on page 25 (at lines 12-18), with the following paragraph:

A2

It has heretofore been thought that the activity ratios of the primary to secondary polymerases should be maintained at 4:1 - 2000:1 for large sequence amplification (*see* U.S. Patent No. 5,436,149). It has now been discovered, however, that in the compositions of the present invention that activity ratios of the primary to secondary polymerases of 1:1, 1:2, 1:4, 1:5, 1:8, 1:10, 1:25, 1:50, 1:100, 1:250, 1:500, 1:1000 and 1:2000 may be suitable for amplification of large nucleotide sequences.

In the Claims:

Please cancel claims 4 and 32 without prejudice to or disclaimer of the subject matter contained therein. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuing or divisional applications.

Please substitute the following claim 1 for pending claim 1:

1. (Once amended) A composition for use in nucleic acid synthesis, nucleic acid amplification, sequencing or restriction digestion, said composition comprising a mixture of reagents at working concentrations, wherein said reagents are at least one thermostable enzyme and at least one buffer salt, and wherein said composition has no nucleic acid molecules.

A3

Please substitute the following claim 2 for pending claim 2:

2. (Once amended) A composition for use in nucleic acid amplification comprising a mixture of reagents at working concentrations, wherein said reagents are at least one thermostable DNA polymerase, at least one buffer salt and at least one deoxynucleoside triphosphate, and wherein said composition has no nucleic acid molecules.

Please substitute the following claim 3 for pending claim 3:

3. (Once amended) A composition for use in nucleic acid sequencing comprising a mixture of reagents at working concentrations, wherein said reagents are at least one thermostable DNA polymerase, at least one deoxynucleoside triphosphate, at least one dideoxynucleoside triphosphate and at least one buffer salt, and wherein said composition has no nucleic acid molecules.

Please substitute the following claim 30 for pending claim 30:

30. (Once amended) A nucleic acid amplification kit comprising one or more containers, wherein a first container contains a composition comprising a mixture of reagents at working concentrations, wherein said reagents are at least one thermostable DNA polymerase, at least one buffer salt, and at least one deoxynucleoside triphosphate, and wherein said composition has no nucleic acid molecules.

A4

Please substitute the following claim 31 for pending claim 31:

31. (Once amended) A nucleic acid sequencing kit comprising one or more containers, wherein a first container contains a composition comprising a mixture of reagents at working concentrations, wherein said reagents are at least one thermostable DNA polymerase, at least one buffer salt, at least one deoxynucleoside triphosphate and at least one dideoxynucleoside triphosphate, and wherein said composition has no nucleic acid molecules.

Please add the following new claims:

48. (New) The composition of claim 1, wherein said composition is stable upon storage.

49. (New) The composition of claim 2, wherein said composition is stable upon storage.

A5

50. (New) The composition of claim 3, wherein said composition is stable upon storage.

51. (New) The nucleic acid amplification kit of claim 30, wherein said composition is stable upon storage.

52. (New) The nucleic acid sequencing kit of claim 31, wherein said composition is stable upon storage.

53. (New) The composition of claim 1, further comprising at least one nonionic detergent.

54. (New) The composition of claim 53, wherein said at least one nonionic detergent is selected from the group consisting of TRITON X-100® , Brij 35, Tween 20 and Nonidet P-40 (NP-40).

55. (New) The composition of claim 27, wherein said at least one nonionic detergent is selected from the group consisting of TRITON X-100® , Brij 35, Tween 20 and Nonidet P-40 (NP-40).

A5

56. (New) The nucleic acid amplification kit of claim 30, further comprising at least one nonionic detergent.

57. (New) The nucleic acid amplification kit of claim 56, wherein said at least one nonionic detergent is selected from the group consisting of TRITON X-100® , Brij 35, Tween 20 and Nonidet P-40 (NP-40).

58. (New) The nucleic acid sequencing kit of claim 31, further comprising at least one nonionic detergent.

59. (New) The nucleic acid sequencing kit of claim 58, wherein said at least one nonionic detergent is selected from the group consisting of TRITON X-100® , Brij 35, Tween 20 and Nonidet P-40 (NP-40).

A5

Remarks

I. Support for Amendments to the Claims

The foregoing amendments to the specification are sought to insert proper cross-reference to the priority information for this application, as required by the Examiner, and to correct a minor typographical error. Therefore, these amendments do not add new matter.

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for the amendments to claims 1-3, 30 and 31 may be found at page 16, lines 20-26, pages 30-33 and throughout the Examples. Support for new claims 48-59 may also be found throughout the specification, specifically at page 16, lines 26-28, page 21, lines 5-16 and page 24, lines 7-13. Accordingly, the present amendments do not add new matter, and their entry is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 4 and 32 have been cancelled without prejudice or disclaimer, claims 1-3, 30 and 31 have been amended, and new claims 48-59 are sought to be entered. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 1-3, 5-31 and 33-59 are pending in the application, with claims 1-3, 30, 31, 34 and 36 being the independent claims.

III. Summary of the Office Action

In the Office Action dated March 22, 2002, the Examiner has made one objection to the specification and nine rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

IV. The Objection to the Specification is Accommodated

In the Office at page 2, section 1, the Examiner has objected to the specification for not including complete priority information. Applicants have amended the specification to include reference to the parent application, as required by the Examiner. Accordingly, the objection has been fully accommodated; reconsideration and withdrawal therefore are respectfully requested.

V. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Traversed

In the Office Action at page 2, section 3, the Examiner has rejected claims 1-3, 30-31 and 44-47 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse this rejection.

In making the rejection, the Examiner contends that:

> [c]laim 1 is indefinite over the recitation of "stable composition" because this term makes the claims unclear with regard to what "stable" is relative. "Stable" does not confer a clear meaning to the composition because the claims to not recite for what the composition is to be used.
>
> Similarly, this claim is indefinite over the recitation of "working concentration" because the meaning of this term is unclear without a recitation describing the kind of "work" the composition is to be used for. The concentration of reagents would be different depending upon the type of "work" to be performed.

Office Action at page 2. Applicants respectfully disagree with these contentions. The term "stable" is clearly defined by the specification, which states that:

> [t]he terms "stable" and "stability" as used herein generally mean the retention by an enzyme of at least 70%, preferably at least 80%, and most preferably at least 90%, of the original enzymatic activity (in units) after the enzyme or composition containing the enzyme has been stored for at least four weeks at a temperature of about 20-25°C, at least one year at a temperature of about 4°C or at least two years at a temperature of -20°C.

Specification, at page 16, line 28, to page 17, line 2. It should be noted that, despite the Examiner's contrary contentions, the term "stable" as used in the context of the claimed invention does not depend on the "kind of 'work' the composition is to be used for" (Office Action at page 2), since this term is defined in the specification with respect to the activity of the particular enzyme(s) present in the composition. As the Federal Circuit has stated, "[i]t is entirely proper 'to use the specification in order to determine what the inventor meant by terms and phrases in the claims.'" *Laitram Corp. v. Morehouse Industries, Inc.*, 143 F.3d 1456, 1462 (Fed. Cir. 1998) (quoting *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1566 (Fed. Cir. 1992). Thus, one of ordinary skill in the art reading the claims, in light of the specification, would easily be able to determine the metes and bounds of these claims. However, solely to advance prosecution and not in acquiescence to the Examiner's rejection, claim 1 does not recite "stable," although such phrase appears in new claims 48-52.

Similarly, the Examiner states that the phrase "working concentration" is allegedly indefinite (*see* Office Action at page 2). Applicants respectfully disagree. The specification states that:

> "working concentration" is used herein to mean the concentration of a reagent that is at or near the optimal concentration used in a

> solution to perform a particular function (such as amplification, sequencing or digestion of nucleic acids.)

Specification at page 16, lines 23-26. However, solely to advance prosecution and not in acquiescence to the Examiner's rejection, claim 1 has been amended to provide non-limiting examples of "the kind of 'work' the composition is to be used for," as suggested by the Examiner. *Id.*

In view of the foregoing remarks, Applicants respectfully assert that claims 1-3, 30-31 and 44-47, particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

VI. The Rejections Under 35 U.S.C. § 102 Are Traversed

In the Office Action at pages 2-5, the Examiner has rejected the present claims under 35 U.S.C. §§ 102(a) or (b). Applicants respectfully traverse these rejections, in view of the following remarks.

A. The Rejection over Scalice

In section 5 of the Office Action, at page 3, the Examiner has rejected claims 1-2, 30 and 44-47 under 35 U.S.C. § 102(b) as being anticipated by Scalice *et al.*, U.S. Patent No. 5,338,671 (Doc. No. AH1, of record; hereinafter "Scalice"). Applicants respectfully traverse this rejection.

Claims 1, 2 and 30 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Scalice does not disclose compositions having no nucleic acid molecules. On the contrary, Scalice's composition described at column 17, relied on by the

Examiner in making this rejection, contains primers and human placental DNA. Accordingly, Scalice fails to disclose the compositions of the present invention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Since Scalice does not expressly or inherently disclose compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules, this reference cannot and does not anticipate claims 1, 2, 30 and 44-47.

In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) over Scalice be reconsidered and withdrawn.

B. The Rejection over Heath

In section 6 of the Office Action, at pages 3-4, the Examiner has rejected claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Heath *et al., Nucl. Acids Res. 21(24)*:5782-5785 (1993) (Doc. No. AS5, of record; hereinafter "Heath"). Applicants respectfully traverse this rejection.

Claims 1 and 2 are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Heath's compositions contain nucleic acid molecules, specifically, oligonucleotides and genomic DNA. *See* Heath at page 5782. Thus, under *Kalman*, Heath cannot and does not anticipate the present claims because Heath does not disclose compositions comprising a mixture of reagents at working concentrations and having no nucleic acid molecules.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Heath.

C. The Rejection over Lundberg

In section 7 of the Office Action, at page 4, the Examiner has rejected claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Lundberg *et al., Gene 108*:1-6 (1991) (Doc. No. AT9, of record; hereinafter "Lundberg"). Applicants respectfully traverse this rejection.

Claims 1 and 2 are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Lundberg's *Pfu* and *Taq* compositions contain nucleic acid molecules, specifically, primers and template DNA. *See* Lundberg at page 4. Hence, under *Kalman* this reference cannot and does not anticipate the claimed invention.

Perhaps recognizing these deficiencies of Lundberg, the Examiner attempts to base this rejection on an inherency argument, stating that this document

> inherently teach[es] the limitation recited in claims 24-25 that the polymerase retains 90% activity for at least for 4 weeks when stored at 20 to 25C and for at least a year when stored at 4C because the composition of the claims and the composition of Lundberg et al. are the same and therefore both compositions have the same characteristics.

Office Action at page 4, section 7. Applicants disagree with these contentions. As previously stated, Applicants' compositions are not identical to Lundberg's compositions. Since, Lundberg does not disclose compositions having no nucleic acid molecules. Therefore, Applicants' compositions are not the same as those of Lundberg, and any rejection based on inherency must necessarily fail.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Lundberg.

D. The Rejection over Barnes

In section 8 of the Office Action, at page 4, the Examiner has rejected claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Barnes *et al., Proc. Natl. Acad. Sci. USA 91*:2216-2220 (1994) (Doc. No. AT1, of record; hereinafter "Barnes"). Applicants respectfully traverse this rejection.

Claims 1 and 2 are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Barnes discloses compositions that have nucleic acid molecules, specifically primers and DNA templates. *See* Barnes at page 2217. Hence, under *Kalman* this reference cannot and does not anticipate the claimed invention because Barnes does not disclose compositions having no nucleic acid molecules.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Barnes.

E. The Rejection over Gelfand

In section 9 of the Office Action, at page 5, the Examiner has rejected claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Gelfand *et al.* , U.S. Patent No. 5,420,029 (Doc. No. AK1, of record; hereinafter "Gelfand"). Applicants respectfully traverse this rejection.

Claims 1 and 2 are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Gelfand's compositions

have nucleic acid molecules, specifically, genomic DNA and primers. *See* Gelfand at col. 35, lines 51-55; col. 36, lines 28-30; and col. 38, lines 41-43. Thus, under *Kalman* this reference cannot and does not anticipate the claimed invention because Gelfand does not disclose compositions having no nucleic acid molecules.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Gelfand.

F. The Rejection over the Kodak PCT

In section 10 of the Office Action, at page 5, the Examiner has rejected claims 1-3, 30 and 31 under 35 U.S.C. § 102(b) as being anticipated by Eastman Kodak, WO 90/08839 (Doc. No. AM1, of record; hereinafter "the Kodak PCT"). Applicants respectfully traverse this rejection.

Claims 1-3, 30 and 31 are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, the Kodak PCT discloses compositions that are not at working concentrations. Specifically, the Kodak PCT discloses "a nucleotide sequencing reaction *concentrate*." The Kodak PCT at page 3, lines 22-23 (emphasis added). The Kodak PCT further discloses an example wherein the concentrate has to be signficantly diluted before use. Specifically, the Kodak PCT states that:

> [i]n a typical reaction, a user provides a quality single-stranded DNA preparation, typically 1 µg (0.4 pmoles) of M13mp18 DNA, at a concentration of >100µg/ml. The user combines the DNA, 5 µl of the Primer/Buffer, water and radioactive nucleotide (usually 1 µCi of ^{32}P or 10 µCi of ^{35}S, alpha-labeled dCTP at >600 Ci/mM), to a total volume of 21 µl. This DNA mixture is divided equally (5 µl) among four tubes (preferably 0.5 ml microfuge tubes), designated for the essential G-, A-, T- and C-specific reactions. These tubes are placed at 70-74°C. Then 2 µl of the appropriate specific Reaction Concentrate is mixed into the designated tubes. The tubes are capped and the incubation continued at the 70-74°C for 30 minutes.

The Kodak PCT at page 18, lines 1-15. Thus, under *Kalman* this reference cannot and does not anticipate the claimed invention because it does not disclose compositions at working concentrations. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over the Kodak PCT.

G. The Rejection over Slatko

In section 11 of the Office Action, at page 5, the Examiner has rejected claims 1-3 under 35 U.S.C. § 102(a) as being anticipated by Slatko *et al., Molec. Biotechnol. 6*:311-322 (1996) (Doc. No. AS13, of record; hereinafter "Slatko"). Applicants respectfully traverse this rejection.

Applicants note that Slatko was published in December 1996. However, the present application is entitled to the filing date of the 35 U.S.C. § 120 priority application, U.S. Application No. 08/689,815, filed August 14, 1996. Hence, Slatko cannot form the basis of a rejection under 35 U.S.C. § 102(a), since it was published after August 14, 1996, the priority date to which the present application is entitled.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(a) over Slatko.

H. Summary

In view of the foregoing remarks, Applicants respectfully assert that none of the cited art anticipates the presently claimed invention under 35 U.S.C. §§ 102(a) or (b). Reconsideration and withdrawal of these rejections are therefore respectfully requested.

VII. The Rejection Under 35 U.S.C. § 103 Is Traversed

In the Office Action at sections 12-13, pages 6-8, the Examiner has rejected claims 31, 45 and 46 under 35 U.S.C. § 103(a) over the Kodak PCT in view of Scalice. Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

Claim 31 is drawn to a nucleic acid sequencing kit comprising compositions having a mixture of reagents at working concentrations and having no nucleic acid molecules. Claim 45 is drawn to compositions having a mixture of reagents at working concentrations, having no nucleic acid molecules and having at least one antibody that binds to a polymerase. Claim 46 is drawn to a nucleic acid amplification kit or nucleic acid sequencing kit comprising

compositions having a mixture of reagents at working concentrations, having no nucleic acid molecules and having at least one antibody that binds to a polymerase. Applicants reiterate and incorporate by reference herein the remarks made above with respect to the Kodak PCT. The Kodak PCT does not disclose, suggest or otherwise contemplate compositions comprising a mixture of reagents at working concentrations. Therefore, the Kodak PCT is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of the Kodak PCT are not cured by the disclosure of Scalice. Scalice does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations and having no nucleic acid molecules. Therefore, the disclosure of the Kodak PCT, alone or in combination with that of Scalice, does not disclose, suggest or contemplate the preparation of nucleic acid-free compositions for nucleic acid amplification or sequencing.

In view of the foregoing remarks, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

VIII. Other Matters

Applicants note that claims 4-29 and 32-43 were not objected to or rejected in the Office Action dated March 22, 2002. Applicants therefore presume that these claims are allowable, despite the Examiner's contention in section 14 at page 8 of the Office Action that "[n]o claims are allowable over the prior art." The Examiner is respectfully requested to clearly indicate the disposition of claims 4-29 and 32-43 on the record in the next communication to Applicants.

IX. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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